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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SITTON, JEHANNE SOUAYA	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,293	HALSTED ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *20-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *1449: 8/2001*.

DETAILED ACTION

Election/Restrictions

1. Claims 20-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response dated August 11, 2003. An action on the merits of claims 1-19 and newly added claim 31 follows.

Specification

2. The specification is objected to for the following reasons:

A) Figure 4 has a part "a" and a part "b", however the brief description of the drawings does not indicate a legend for each part of the figure.

B) On page 18, the specification incorrectly references figure 3 at lines 29 and 30. Since there is no figure 3a,b, or c, it appears that the specification should cite figure 2 instead.

C) There are nucleotide sequences in the specification that are not designated by an appropriate sequence identifier (see for example page 26). All nucleic acid and amino acid sequences iterated in the specification must have appropriate sequence identifiers as outlined in Chapter 2400 of the MPEP.

D) The sequence of the GCPII cDNA is considered essential material in the instant specification as the claims contain a mutation with numbering directly resultant from the sequence. The MPEP states:

> It is therefore essential that all sequence information, whether only disclosed or also claimed, be included in the database. In those instances in which prior art sequences are only referred to in a given application by name and a publication or accession reference, they need not be included as part of the "Sequence Listing," unless an examiner considers the referred- to sequence to be "essential material," per MPEP § 608.01(p).

Applicants should amend the sequence listing to reflect such sequence. Such sequence should be the cDNA that was available and cited by the specification in Genbank. Applicants should take care not to use any updated sequences, should any exist, as such would enter new matter into the specification. A statement to that effect should accompany the submission of the sequence listing (see MPEP: 2422.03)

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-19 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands,* 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

Nature of the Invention

The claims are broadly drawn to screening an individual for increased risk of low folate status by detecting any mutation in a GCPII gene wherein detection of the mutation is indicative of a decreased ability to hydrolyze a terminal glutamate residue of a folylpoly-γ- glutamate which decreased ability is associated with low folate status. The claims are further drawn to detecting any such mutation in exon 13 of a GCPII gene, also drawn specifically to a single nucleotide polymorphism that causes an amino acid substitution of H475Y, and further drawn to such mutations being further indicative that an individual is at increased risk of hyperhomocysteinemia. The claims are also drawn to screening an individual for increased risk of low folate status by detecting a variant product in which 93 bases of exon 18 are deleted and determining the ratio of variant to normal product wherein a ratio of variant to product greater than 1:3 is indicative that the individual is at increased risk of low folate status.

Amount of direction and guidance

The specification teaches that several studies have described correlations between low folate status, hyperhomocysteinemia and dementia in aging Caucasian patients with Alzheimer's disease and that a recent English study found significantly lower serum and red blood cell (RBC) folate levels and higher serum homocysteine levels in a patient population of 164 patients with Alzheimer's disease compared to 108 age matched controls. (see page 3, lines 5-15). The specification defines "low folate status" as referring to an individual with folate levels which are associated with increased levels of homocysteine, and increased risk of colon cancer, cognitive defects such as Alzheimer's disease, and women at increased risk of bearing children with neural tube defects or congenital heart defects (see page 9, lines 25-28). The specification teaches that

folylpoly-γ-glutamate carboxypeptidase (FGCP), expressed in human small intestine, is responsible for the hydrolysis of terminal glutamate residues in folylpoly-γ-glutamates, and plays an important role in availability of dietary folates (see para bridging pages 1and 2). The specification teaches that recent molecular characterization has supported the concept that FGCP, NAALADase (N-acetylated-a-linked acidic dipeptidase, a brain enzyme), and PMSA (Prostate specific membrane antigen) represent functionally distinct expression of a single gene that encodes 750 amino acids and is collectively known as glutamate carboxypeptidase II (GCPII) (lines 10-31, page 3 of specification). The specification teaches that the cDNA sequence of human intestinal GCPII has complete identity to human PSMA and NAALADase with some exceptions (see page 6, lines 5-10).

The specification does not teach the sequence of the GCPII gene. Further, it appears that the sequence of the gene was not known in the art at the time the invention was filed.

Presence and absence of Working examples

The specification teaches that a splice variant of GCPII in human jejunum, which lacks exon 18, has been found and lacks 93 nucleotides present in the normal expression product. The specification teaches that the intestinal FGCP enzyme translated from this splice variant is inactive in hydrolyzing the conjugated folates which are the majority of folates present in the diet (see page 6, lines 11-17). The specification asserts that while the splice variant is present in some degree in all individuals, persons that have a higher ratio for splice variant to wild type transcript (i.e.: 1:1.5, 1:2, or 1:2.5) than individuals with normal ratios are less capable than the majority of persons at cleaving the terminal glutamates from dietary folates and therefore less likely to be able to satisfy their needs for folate from dietary folates alone. The specification

further asserts that such persons are therefore more likely to require supplementation with folic acid and in the absence of such are at increased risk for low folate status, hyperhomocysteinemia, cardiovascular disease, colon cancer, and altered cognition including Alzheimer's disease in the elderly (see page 6). The specification, however, does not teach a study that tested the effect of such ratio on serum folate or homocysteine levels, nor teaches any examples of individuals with any of the diseases listed above with an abnormal ratio of altered : wildtype transcript.

The following are unclear from the teachings in the specification. The specification does not teach how human intestinal FGCP, PSMA, and NAALADase are different. Further, it is unclear if when referring to the "splice variant transcript" and "wildtype transcript", the specification is referring to intestinal FGCP. Further, it is unclear if human intestinal GCPII is in fact the same protein as FGCP. It appears that when referring to "mutations in a human GCPII gene" (for example claim 1), mutations resulting in altered PSMA and NAALADase proteins are encompassed by the recitation. However, the specification has not taught or described any examples that correlated alterations or mutations in PSMA or NAALADase and serum or RBC folate levels or homocysteine levels.

The specification teaches a study that identified a potentially significant mutation in GCPII (leading to a H475Y substitution in exon 13) in a previous study of aging Caucasian subjects. The study found no significant association between the mutation and either homocysteine levels or serum folate levels in Alzheimer's patients from the study, however. The study did find a statistically significant association between the mutation and lower serum folate levels ($p<0.001$, p 23) and less significant association ($p<0.05$) with elevated homocysteine levels in the study population as a whole. Further, the specification teaches that in vitro analysis

of the H475Y mutation showed that in transfected COS-7 cells with the cDNA mutant expressed less than 50% of wildtype FGCP activity in membranes (pages 23-25). Such findings lead the specification to assert that mutations in GCPII affecting the activity of FGCP would predictably decrease folate levels in the body.

Predictability and unpredictability of the art

The art, however, teaches studies that conflict with the findings taught in the specification with regard to the H475Y mutation in GCPII. For example, Martinez (Vargas-Martinez et al; Journal of Nutrition, 2002, vol 132, pp 1176-1179) teaches analysis of the effect of the 1561 C to T (encodes the H475Y mutation in exon 13 of GCPII) mutation on folate and homocysteine levels in a larger study of patients, the Framingham Offspring Cohort (see abstract). It is further noted that Martinez specifically cites the results of the study in the instant specification and acknowledges the association with lower serum folate levels and lower in vitro enzyme activity of the mutant in the work of Devlin et al, Hum. Mol. Genet, vol. 9, pp 2837-2844, 2000, which is the identical analysis set forth in the instant specification. Martinez contrasts their study with that of Devlin in that the population cohort of Martinez was larger than that of Devlin (1913 subjects, 200 of whom had the T allele compared to 75 subjects, only 6 of which were heterozygous for the T allele in the Devlin study) and that the Martinez cohort was a well characterized cohort representative of the general population in whom dietary habits and other lifestyle and biochemical variables have been extensively documented (see page 1176, col. 2, 4th para). In contrast to the analysis of the instant specification, Martinez teaches that the GCPII T allele was not associated with lower plasma folate concentration or higher plasma total homocysteine levels (see page 1178, para bridging cols 1 and 2). Martinez further teaches that

"if anything, male carriers of the mutation had significantly higher folate concentrations than men homozygous for the wildtype allele". With regard to an association in women, Martinez teaches that no differences in plasma folate or total homocysteine levels for the C or T allele. Martinez concludes that in the Framingham cohort, the polymorphism is inconsequential as far as folate and total homocysteine plasma levels are concerned (see page 1179, col 1). Plassmann (Sunder-Plassmann et al; Kidney International. Supplement. May 2003, vol. 84, pp s141-144) provides a review of the effects of the GCPII C to T polymorphism on folate and homocysteine levels. Plassmann teaches that among Italian neural tube defect patients, there was a *decreased* frequency of the GCPII T mutant (see p 143, col. 1, para4), which contrasts the specification's assertion that patients with the allele are more susceptible to low folate status which is also associated with neural tube defects. Plassmann also teaches that in a study of 190 vascular disease patients and 601 controls, the mutant T allele was associated with *elevated* red blood cell folate and plasma folate levels and that no association with cardiovascular disease or plasma total homocysteine levels was observed for the T allele, again in contrast to the assertion in the specification that patients with the T allele are more susceptible to low folate status which is also associated with cardiovascular disease. Thus, as is evidenced by the post filing date art, no predictable association can be made with low serum folate and generally mutations that lead to decreased FGCP activity, elevated levels of total homocysteine, or patients with neural tube defects or cardiovascular disease. Further, as is evidenced by the teachings in the specification, no predictable association was made with regard to the presence of the mutant H475Y GCPII, low serum folate and Alzheimer's disease. In addition, the art does not teach of any association

between the GCPII transcript lacking exon 18, and serum folate levels, total homocysteine levels, or any of the diseases associated with low folate status in the specification.

Quantity of Experimentation Necessary

Given the lack of guidance in the specification with regard to an association between the mutant GCPII transcript lacking exon 18 and patients with low folate status, and the unpredictability taught in the specification and the art with regard to a predictable association between the presence of the GCPII 1561 T allele and low serum folate, elevated homocysteine, neural tube defects, cardiovascular disease, and Alzheimer's disease, the skilled artisan would have to perform an extremely large study in different populations do determine if in fact there was either an association between the GCPII transcript lacking exon 18, or the GCPII 1561 T allele, or generally any mutation that affected the hydrolysis of terminal glutamates in folylpoly-γ-glutamates, and lowered serum folate levels, elevated homocysteine levels, low folate status, neural tube defects, cardiovascular disease or Alzheimer's disease. The results of such a study are completely unpredictable as evidenced by the conflicting evidence presented in the specification and the post filing date art (which reflects the current state of the art) with regard to the 1561 T allele and serum folate and homocysteine levels in healthy individuals as well as those with neural tube defects, cardiovascular disease or Alzheimer's disease. The claims are broadly drawn to screening individuals for mutations in a gene, whose complete sequence was not known in the art at the time of the invention, as well as altered transcripts of the gene. Further, the claims are drawn to such mutations affecting the ability to hydrolyze a terminal glutamate residue of a folylpoly-γ-glutamate. To practice the invention as broadly as it is claimed, the skilled artisan would have to determine the sequence of the GCPII gene and then

determine which mutations would be associated with such decreased activity. Such mutations, however do not predictably alter serum folate or homocysteine levels, as evidenced by the teachings of the post filing date art. The skilled artisan would then have to screen mutations to determine those that affect folate and homocysteine levels and then would have to perform an extremely large amount of trial and error analysis in a large study to determine if such mutations would predictably affect lower serum folate and elevated homocysteine levels in different healthy and diseased populations. Given the lack of guidance in the specification and the conflicting evidence in the art, such analysis is replete with unpredictable experimentation, and is considered undue.

Conclusion

5. No claims are allowable.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

Note: The examiner's name has changed from Jehanne Souaya to Jehanne Sitton. All future correspondence to the examiner should reflect the change in name. It is also noted that after January 12, 2004, the examiner will be located at the new USPTO campus and will be reachable at telephone number (571) 272-0752.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne (Souaya) Sitton
Primary Examiner
Art Unit 1634

Jehanne Sitton
12/1/03